SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

HYDRALAZINE FC 50

2. Qualitative and quantitative composition

Each tablet contains 50 mg hydralazine hydrochloride.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet

Pink, round, biconvex film-coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of moderate to severe hypertension as an adjunct to other antihypertensive agents.

Due to the complementary mechanism of action the combination of hydralazine with β-blockers and diuretics may enable antihypertensive efficacy at lower dose levels and counteract accompanying hydralazine effects such as reflex tachycardia and oedema.

As supplementary medication for use in combination with long-acting nitrates in moderate to severe chronic congestive cardiac failure in patients in whom optimal doses of conventional therapy have proved insufficient.

4.2 Posology and method of administration

Posology

The dosage should be adjusted to the individual requirements of the patient. Treatment should commence with low doses which, depending on the patient's response, should be increased stepwise to achieve optimal therapeutic effect, whilst minimising unwanted effects.

Adults:

Hypertension: the initial dose is 25 mg twice daily. This may be increased gradually to a maximum dose of 200 mg daily. The patient's acetylator status must be checked prior to increasing the daily dose beyond 100 mg.

Chronic congestive heart failure: Doses vary greatly between individual patients and are generally higher than those used to treat hypertension. Treatment should be initiated in hospital where the patient's individual haemodynamic values can be determined with the help of invasive monitoring. Treatment should continue in hospital until the patient has been established on the required maintenance dose. After progressive titration (initially 25 mg three or four times daily, increasing every second day) maintenance dosage averages 50-75 mg four times daily.

Children:

Hydralazine is not recommended.

Elderly:

There is no special dosage requirement. Systemic clearance and blood concentration of hydralazine are not affected by advanced age, though renal elimination may be affected due to diminished kidney function with age. The elderly may also be more sensitive to the hypotensive effects of hydralazine.

Method of administration

For oral administration only. Swallow the tablets with a glass of water.

4.3 Contraindications

Hydralazine is contraindicated in patients with:

- Hypersensitivity to the active substance, dihydralazine or to any of the excipients listed in section 6.1
- Idiopathic systemic lupus erythematosus (SLE) and related diseases
- Severe tachycardia
- High output cardiac failure (e.g. in thyrotoxicosis)
- Myocardial insufficiency due to mechanical obstruction (e.g. in the presence of mitral or aortic stenosis or constrictive pericarditis)
- Cor pulmonale
- Dissecting aortic aneurysm
- Porphyria

4.4 Special warnings and precautions for use

Warnings

The “Hyperdynamic” state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate angina pectoris. Patients with suspected or confirmed coronary artery disease should be given Hydralazine only under cover of a beta-blocker or in combination with other suitable sympatholytic agents. Beta-blocker medication should be started a few days prior to commencing treatment with Hydralazine.

Patients who have survived a myocardial infarction should not receive Hydralazine until a post-infarction stabilization phase has been achieved.

Prolonged treatment with Hydralazine (i.e. usually for more than 6 months) may provoke a systemic lupus erythematosus (SLE) like syndrome, especially with doses exceeding 100 mg daily. Initial symptoms are likely to be similar to rheumatoid arthritis (arthralgia, sometimes associated with rash, anaemia, leucopenia, thrombocytopenia and fever) and are reversible upon withdrawal of the drug. In its more severe form, it resembles acute SLE (similar manifestations as the milder form plus pleurisy, pleural effusions and pericarditis), and in rare cases renal and ocular involvement have been reported. Early detection and a timely diagnosis with appropriate therapy (i.e. treatment discontinuation and possibly long-term treatment with corticosteroids may be required to reverse these changes) are of utmost importance in this life-threatening illness to prevent more severe complications, which may sometimes be fatal.

Since such reactions tend to occur more frequently with higher doses and longer duration of treatment and since they are also more common in slow acetylators, the lowest effective dose should be used for maintenance therapy. If 100 mg daily fails to elicit an adequate response, the patient's acetylator status should be evaluated. Slow acetylators and women are at greater risk of developing the SLE-like syndrome and every effort should therefore be made to keep the dosage below 100 mg daily. The patient should be watched for signs and symptoms of the syndrome and if such symptoms develop, the drug should be gradually withdrawn. Rapid

acetylators often respond inadequately even to doses of 100 mg daily and therefore the dose may be raised with only a slightly increased risk of an SLE-like syndrome.

During long-term treatment with Hydralazine, it is advisable to determine the antinuclear factors and conduct urine analysis at intervals of approximately 6 months. Microhaematuria and /or proteinuria, in particular along with positive ANF titres, may be initial signs of immune-complex glomerulonephritis associated with the SLE-like syndrome. If overt clinical signs or symptoms develop, Hydralazine should be withdrawn immediately.

Skin rash, febrile reactions and change in blood count occur rarely and the drug should be withdrawn. Peripheral neuritis in the form of paraesthesia has been reported and may respond to pyridoxine administration or withdrawal of the drug.

Precautions

Hydralazine dose or interval between doses should be adjusted according to clinical response in patients with hepatic dysfunction or renal impairment (creatinine clearance < 30 ml/ min or serum creatinine > 2.5 mg/ 100 ml) in order to avoid accumulation of the drug.

Hydralazine should be used with caution in patients with coronary artery disease (since it may increase angina) or cerebrovascular disease.

Patients on Hydralazine who undergo surgery, may show a fall in blood pressure. Adrenaline should not be used to correct the hypotension since it enhances the cardiac-accelerating effects of hydralazine.

When initiating therapy in heart failure, particular caution should be exercised, and the patient monitored for early detection of postural hypotension or tachycardia. Where discontinuation of therapy in heart failure is necessary, Hydralazine should be withdrawn gradually (except in serious situations such as SLE-like syndrome or blood dyscrasias) in order to avoid precipitation and /or exacerbation of heart failure.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The following drugs enhance the hypotensive effects of hydralazine:

- Other antihypertensives (diuretics, ACE inhibitors, calcium channel blockers, vasodilators*)
- Anaesthetics
- Tricyclic antidepressants
- Major tranquillisers
- Nitrates or drugs exerting central depressant actions (including alcohol)

**Administration of Hydralazine within an hour or two of diazoxide may give rise to marked hypotension.*

The following drugs antagonise the effects of hydralazine:

- Non-steroidal anti-inflammatory agents (especially indometacin)
- Corticosteroids
- Carbenoxolone
- Oestrogens and combined oral contraceptives

Concurrent administration of hydralazine and beta-blockers which are subject to significant first-pass metabolism (e.g. propranolol) may result in increased bioavailability of the beta-blocker. Dosage reduction of the beta-blocker may be necessary in such cases.

MAOI's should be used with caution in patients receiving hydralazine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Hydralazine readily crosses the placenta with serum concentrations in the foetus being equal to or greater than those in the mother. Animal studies have shown reproductive toxicity (see section 5.3). No serious adverse effects in human pregnancy have been reported with hydralazine use during the third trimester. Thrombocytopenia, leucopenia, petechial bleeding and haematomas have been reported in new-borns whose mother took hydralazine, though these symptoms resolved spontaneously in one to three weeks. Hydralazine should be avoided during the first and second trimesters of pregnancy but may be used later in pregnancy if the mother or foetus is at risk (e.g. pre-eclampsia, eclampsia) or if no safer alternative is available.

Breast-feeding

Hydralazine passes into breast milk but reports to date have not indicated adverse effects on the infant. Breast-fed infants of mothers taking hydralazine should be observed for possible adverse effects.

4.7 Effects on ability to drive and use machines

Hydralazine may cause headache and difficulty in concentration, especially at the start of treatment, which can impair the patient's reactions. If symptoms are severe, the patient should not drive or operate machinery.

4.8 Undesirable effects

Some side effects of hydralazine such as palpitations, tachycardia, angina symptoms, flushing, headaches, dizziness, gastrointestinal disturbances and nasal congestion are commonly seen at the start of therapy especially if the dose is raised quickly but generally subside as treatment continues.

Adverse reactions are categorised by frequencies as follows: very common (≥1/10), common (≥1/100 to <1/10), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

Blood and lymphatic system disorders:

Rare: leucopenia, neutropenia, thrombocytopenia with or without purpura, anaemia

Very rare: haemolytic anaemia, lymphadenopathy, leucocytosis, pancytopenia, splenomegaly and agranulocytosis

Immune system disorders:

Rare: hypersensitivity reactions such as urticaria, pruritus, vasculitis, eosinophilia, hepatitis

Psychiatric disorders:

Rare: anorexia, agitation, anxiety

Very rare: depression, hallucinations

Nervous system disorders:

Very common: headache

Common: dizziness

Very rare: peripheral neuritis, polyneuritis and paraesthesia (which may be reversed by administering pyridoxine)

Cardiac disorders:

Very common: palpitations and tachycardia

Common: angina symptoms

Rare: heart failure

Very rare: paradoxical pressor responses

Vascular disorders:

Common: hypotension, flushing

Respiratory, thoracic and mediastinal disorders:

Common: nasal congestion

Rare: dyspnoea and pleural pain

Eye disorders:

Rare: increased lacrimation, conjunctivitis

Very rare: exophthalmos

Gastrointestinal disorders:

Common: gastrointestinal disturbances, diarrhoea, nausea and vomiting

Very rare: paralytic ileus

Hepatobiliary disorders:

Rare: jaundice, hepatomegaly, abnormal liver function sometimes in association with hepatitis

Skin and subcutaneous tissue disorders:

Rare: skin rash

Musculoskeletal and connective tissue disorders:

Common: arthralgia, myalgia, joint swelling, SLE-like syndrome (sometimes resulting in a fatal outcome, see section 4.4)

Renal and urinary disorders:

Rare: proteinuria, haematuria sometimes associated with glomerulonephritis

Very rare: acute renal failure and urinary retention

General disorders and administration site conditions:

Rare: fever, weight loss, malaise, oedema

Investigations:

Rare: increased plasma creatinine

4.9 Overdose

Symptoms

The signs and symptoms of hydralazine overdose include hypotension, tachycardia, headache and generalised skin flushing. Complications can include myocardial ischemia and subsequent myocardial infarction, cardiac arrhythmias, profound shock and coma.

Management

There is no specific antidote. Gastric lavage should be instituted as soon as possible, taking adequate precautions against aspiration and for protection of the airway. An activated charcoal slurry may be instilled if conditions permit. These procedures may have to be omitted or carried out after cardiovascular status has been stabilised since they might precipitate cardiac arrhythmias or increase the depth of shock.

Support of the cardiovascular system is of primary importance. Shock should be treated with plasma expanders if possible, rather than vasopressors. Supportive measures including intravenous fluids are also indicated. If hypotension is present, an attempt should be made to raise the blood pressure without increasing the tachycardia. If a vasopressor is used, one should be chosen that is least likely to precipitate or aggravate cardiac arrhythmia. Tachycardia responds to beta-blockers. Digitalisation may be necessary. Fluid and electrolyte status and renal function should be monitored.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Arteriolar smooth muscle, agents acting on; hydrazinophthalazine derivatives, ATC Code: C02DB02

Mechanism of action

Hydralazine is a direct acting vasodilator which exerts its effects primarily on the arterioles, with little effect on veins. Its exact mechanism of action is unknown.

Pharmacodynamic effects

Administration of hydralazine decreases peripheral resistance and arterial blood pressure, producing a reflex increase in heart rate and cardiac output. These reflex effects can be reduced by concomitant administration of a beta-blocker, thus enhancing the antihypertensive effect. Increased plasma renin activity and sodium and water retention, producing oedema and reduced urinary volume, may also occur with hydralazine administration attenuating its antihypertensive action. These effects can be prevented by concomitant administration of a diuretic.

5.2 Pharmacokinetic properties

Absorption

Hydralazine is well absorbed (up to 90%) after oral administration but is subject to a dose-dependent first-pass effect. Systemic bioavailability ranges from 26-55% and is dependent on individual acetylator status. Food may enhance the bioavailability of hydralazine by reducing first-pass metabolism in the gut wall. Peak plasma concentrations are reached after 0.5 – 1.5 hours.

Distribution

Hydralazine is rapidly distributed in the body and displays a particular affinity for the blood vessel walls. It is highly protein bound (≈ 90%) in the plasma. Within 24 hours after an oral dose, the quantity recovered in the urine averages 80% of the dose.

Elimination

Hydralazine appears in the plasma chiefly in the form of a readily hydrolysable conjugate with pyruvic acid. Its plasma half-life averages 2-3 hours but is prolonged up to 16 hours in severe renal failure (creatinine clearance < 20 ml/ min) and shortened to approximately 45 minutes in rapid acetylators.

The bulk of the dose excreted as acetylated and hydroxylated metabolites, some of which are conjugated with glucuronic acid.

5.3 Preclinical safety data

Studies in animals found hydralazine to be teratogenic in mice at oral doses ranging from 20 – 120 mg/kg (20-30 times the maximum human daily dose). Teratogenic effects included cleft palate and malformations of facial and cranial bones. Hydralazine was not found to be teratogenic in rats or rabbits.

In high (cyto-) toxic concentrations, hydralazine induces gene mutations in single cell organisms and in mammalian cells in vitro. No unequivocally mutagenic effects have been detected in-vivo in a great number of test systems.

In lifetime carcinogenicity studies, hydralazine, towards the end of the experiments, caused small but statistically significant increase in lung tumours in mice and hepatic and testicular tumours in rats. These tumours also occur spontaneously with fairly high frequency in aged rodents.

With due consideration of these toxicological findings, hydralazine in therapeutic doses does not appear to bear a risk that would necessitate a limitation of its administration.

Years of clinical experience have not suggested that the use of hydralazine is associated with any risk of cancer in humans.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Mannitol powder

Corn starch

Povidone

Edetate disodium

Colloidal silicon dioxide

Magnesium stearate

Tablet coat

Hypromellose

Titanium dioxide

Polyethylene glycol 6000

Erythrosine lake

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C. Keep in the original package in order to protect from light.

6.5 Nature and contents of container

Primary packaging is an opaque white Polyvinylidene chloride (PVDC)-coated Polyvinyl chloride (PVC) film covered with aluminium sheet (PVC/PVDC blister). The secondary packaging is a paper carton.

Each pack type is available in pack sizes of 12 blisters x 10 tablets and 50 blisters x 10 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

T.O.PHARMA CO., LTD.
101 Soi Ladprao 124 (Sawatdikan),
Ladprao Road, Phlapphla, Wangthonglang,
Bangkok 10310,Thailand

8. Date of revision of the text

July 2024